

SUPPORT FOR THE AMENDMENTS

Claim 1 has been amended.

Support for the amendment of Claim 1 is provided by the previously pending corresponding claim, as well as the specification as originally filed, for example at page 4, lines 12-25 and Example 4.

No new matter has been introduced by the present amendment.

REMARKS

Claims 1-41 are pending in this application.

The rejection of Claims 1-4, 12-20, 24-25, and 33-41 under 35 U.S.C. §103(a) over Hofrichter et al is traversed.

At the outset, Applicants direct the Examiner's attention to the fact that Hofrichter et al fails to provide any suggestion of the subject matter of Claims 24-41 (i.e., *n-acyl aspartic acid derivatives*). The only mention in the disclosure of Hofrichter et al of n-acyl aspartic acid derivatives appears in column 4, lines 28-31, which states: "n-acyl amino acid derivatives include n-acyl amino acid amides and n-acyl amino acid esters prepared from glutamic acid, lysine, glutamine, aspartic acid and mixtures thereof."

MPEP §2142 states: "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation... to modify the reference... Second, there must be a reasonable expectation of success. Finally, the prior art reference... must teach or suggest all the claim limitations." Clearly the statement above taken from Hofrichter et al is insufficient on its own to support a *prima facie* case of obviousness. Further, Applicants note that the Examiner has failed to provide any explanation whatsoever to support and/or indicate how and why the present invention as claimed in Claims 24-41 would allegedly be obvious in view of the disclosure of Hofrichter et al.

In view of the foregoing, Applicants submit that the rejection of Claims 24-41 over Hofrichter et al is not tenable and should be withdrawn.

Turning to Claims 1-23, Applicants note that Hofrichter et al disclose an antiperspirant gel stick containing a gelling agent selected from 12-hydroxystearic acid, esters of

12-hydroxystearic acid, amides of 12-hydroxystearic acid, and mixtures thereof as a primary gelling agent and an n-acyl amino acid amide derivative as a secondary gelling agent (see Abstract).

The Examiner points to the very broad disclosure of n-acyl amino acid amide derivative provided in column 4, lines 35-43. The Examiner then asserts that all of the claimed compounds are encompassed by the generic formula taught in Hofrichter et al. Applicants note that although Hofrichter et al. may provide for the possibility of a compound within the scope of the claimed invention, Hofrichter et al. fail to provide adequate motivation to select such a compound from the very broad genus disclosed therein, much less provide a reasonable expectation of the advantageous properties flowing therefrom. In fact, the Examiner has acknowledged the absence of a specific disclosure in Hofrichter et al. of the claimed invention noting: "applicant's claims require narrower scope than what US '424 suggests in his generic formula (column 4, lines 35-43) and US '424 fails to specifically mention the same species required by instant claims 3-4." (paper number 8, page 4, lines 19-21)

Not only do Hofrichter et al. fail to explicitly name, suggest, or exemplify any species that falls within the scope of the present claims, the preferred species listed by Hofrichter et al. at column 4, line 52 to column 5, line 2 would actually lead the artisan away from the range of  $R^3$  in the present claims. As such there can be no motivation to select or obtain the claimed compounds (having  $R^3$  represents a hydrocarbon group having 8 to 10 carbon atoms) from the broad genus of Hofrichter et al. This is particularly true when the artisan inspects the preferred species of Hofrichter et al. at column 4, line 52 to column 5, line 2 and the Examples, in which the position corresponding to  $R^3$  contains 11 carbon atoms or more. Moreover, based on the disclosure of Hofrichter et al. the skilled artisan would have no means of envisioning the advantages flowing from the claimed invention as demonstrated in the present specification and highlighted in the Amendment and Request for Reconsideration filed on November 25,

2003 and June 10, 2004 (reproduced herein below) and further supported by the Declaration under 37 C.F.R. §1.132 **submitted herewith**.

It is the Examiner's position that the claimed range of  $R^3 = C_{8-10}$  is *prima facie* obvious in view of the disclosure by Hofrichter et al, which happens to include, amongst a broad genus, an n-acyl glutamic acid amide derivative in which the position corresponding to  $R^3 = C_{1-26}$ . Applicants note that it has been long held (see MPEP §§716.02-716.02(f)) that a *prima facie* case of obviousness can be overcome by a demonstration of unexpected results flowing from a claimed narrow range versus a broader range disclosed by the prior art (i.e., Hofrichter et al). Despite the clear evidentiary showing of unexpected results provided by Applicants in the present specification, the Examiner has maintained this rejection. Specifically, Applicants note that, as again noted below, the present specification compared the closest prior art compound to the compounds of the claimed invention that most closely approach that prior art compound. These data clearly show the superior gelling effect provided by the claimed compounds, as exemplified by N-2-ethylhexanoylglutamic acid dibutylamide, compared to N-lauroylglutamic acid dibutylamide, which represents Hofrichter et al, as well as the superior gelling ability of N-decanoylglutamic acid dibutylamide (Example 6 of the present invention) compared to N-lauroylglutamic acid dibutylamide (Hofrichter et al).

The Examiner disregards this evidence asserting that the unexpected superior gelling effect corresponds to an intended use and not the compound. Applicants disagree with this assertion by the Examiner. As is widely appreciated, a prominent way to demonstrate an unexpected property for a compound is by placing the compound into context by comparing the behavior of the compound of interest with a control compound under certain conditions and monitoring a specific property. In the present application, this comparison has been accomplished, for example, by preparing antiperspirant gel sticks that differ only by the n-acyl

glutamic acid derivative employed and measuring the resulting gel strength using a rheometer (see below). Accordingly, the assay established is a single variable assay in which the variable *is* the n-acyl glutamic acid derivative. Therefore, the unexpected properties arising therefrom *are necessarily* related to the n-acyl glutamic acid derivative.

The aforementioned method of demonstrating nonobviousness is not new and finds support in the case law. The Examiner is directed to *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) and *In re Papesch*, 137 USPQ 43 (CCPA 1963), copies submitted with response filed on June 10, 2004. In *Ex parte A* unexpected superior therapeutic activity of the *claimed compound* against anaerobic bacteria (*i.e.*, intended use) was sufficient to rebut *prima facie* obviousness even though there was no evidence that the compound was effective against all bacteria. In *In re Papesch*, the rejection of the claims to a *compound* structurally similar to the prior art compound was reversed because the claimed compound unexpectedly possessed anti-inflammatory properties (*i.e.*, intended use) not possessed by the prior art compound. Therefore, as in *Ex parte A* and *In re Papesch* the evidentiary showing of unexpected results of the claimed compound is sufficient to rebut the *prima facie* case of obviousness.

For the Examiner's convenience, the following analysis/summary of the comparative data between the claimed invention and the disclosure of Hofrichter et al is reproduced from the Amendment and Request for Reconsideration filed on November 25, 2003 and June 10, 2004:

The presently claimed compounds have a high gelling ability in various types of oils. In particular, the presently claimed compounds can result in high values far exceeding 100 as shown in Table 1 for IPM (isopropyl myristate), TOG (triocanoic acid glyceride), and liquid paraffin. In this connection, a higher gelling value corresponds to a higher gelling ability to obtain a hard gel. Accordingly, a gelling ability lower than 100 is insufficient for preparation of a hard gel, such as is necessary for preparation of a lipstick. Therefore, the advantageous

effect of the present invention can be understood in that the compounds have a high gelling ability for various kinds of oils and, as a result, can give hard gels suitable for preparation of lipsticks having a resistance to breakage.

The advantages provided by the presently claimed invention can be seen by a direct comparison between a preferred compound from Hofrichter et al (N-lauroylglutamic acid dibutylamide; Comparative Example 3) and the closest compound within the scope of the present invention (N-decanoylglutamic acid dibutylamide; Example 6). In this comparison 0.1g of each N-acyl glutamic acid dibutylamide was added to 20g of each oil. The N-acyl glutamic acid dibutylamide was then dissolved by heating on an oil bath at 150°C. The resulting solution was cooled for 15 hours at 23°C to obtain a gel composition. Subsequently, gel strength of each of the resulting gel compositions was measured by using a rheometer (page 13, lines 6-16).

The gelling ability of each of these compounds was determined for IPM (isopropyl myristate), TOG (trioleic acid glyceride), and liquid paraffin as described above and the results are reported in Table 1, which is reproduced in relevant part below:

Gel composition	Acyl group	IPM	TOG	Liquid paraffin
Example 6 (present invention)	Decanoyl	120	183	154
Comparative Example 3 ( <u>Hofrichter et al</u> )	Dodecanoyl (lauroyl)	95	116	92

What is clear from the above is that, for each of the oils tested, the claimed N-acylglutamic acid dibutylamides provide superior gelling activity irrespective of the oil selected. Such a result certainly is not apparent from the disclosure of Hofrichter et al.

Further, the N-lauroylglutamic acid dibutylamide, which is a typical example from Hofrichter et al and has a long-chain acyl group (compound A), was tested in Comparative Example 9 in the present specification. The exemplary Hofrichter et al compound was compared to a compound within the scope of the presently claimed invention: an N-2-ethylhexanoylglutamic acid dibutylamide (Example 12), i.e., a compound having a short acyl group. In this comparison, each gelling agent was dissolved in an oil by heating, then aluminum zirconium trichlorohydrate glycine was added to the resulting solution, and the solution was cooled with stirring to obtain an antiperspirant gel stick. Gel strength of each of the resulting antiperspirant gel sticks was measured by using a rheometer (page 16, lines 1-10). The results appear in Table 3, which is reproduced in its entirety below. Also appearing in Table 3 are the additional additives that were present in the antiperspirant gel sticks, which were maintained at a constant value to ensure that the only variable for comparison is the amount of the gelling agent.

	Comparative Example 9	Example 11	Example 12
N-lauroylglutamic acid dibutylamide	2	1	-
N-2-ethylhexanoylglutamic acid dibutylamide	-	1	2
12-Hydroxystearic acid	7	7	7
Octyldodecanol	14	14	14

Cyclometicon D-5	48	48	48
Aluminum zirconium trichlorohydrate glycine	26	26	26
Gel strength (g/cm <sup>2</sup> )	1847	2250	2650

In Table 3, the compound within the scope of the presently claimed invention (Example 12), having a shorter and branched acyl group, provided a significantly improved gel strength (g/cm<sup>2</sup>) compared to the preferred compound of Hofrichter et al, which has a long-chain acyl group. From Table 3, it can be readily understood that the compound of the present invention with a shorter acyl group has improved gelling properties than that of the prior known compounds having a long-chain acyl group.

Moreover, with regard to the advantageous effect of the present invention, Applicants note that the combination of the presently claimed compound (exemplified by N-2-ethylhexanoylglutamic acid dibutylamide having a short acyl group) with N-lauroylglutamic acid dibutylamide can produce even greater gelling ability (preferably when used in a 1:1 ratio) as compared to just N-lauroylglutamic acid dibutylamide alone. In particular the 1:1 ratio is superior for providing a translucent gel.

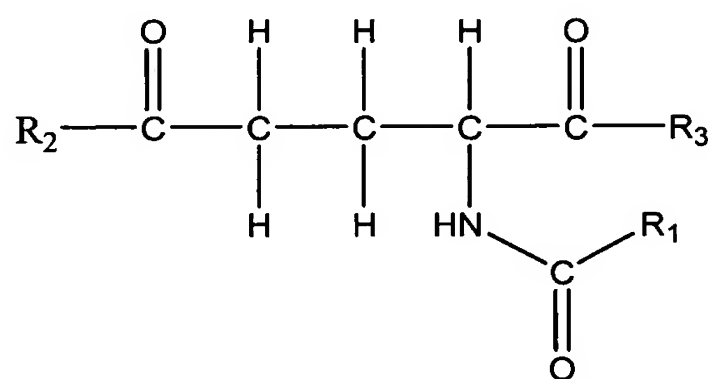
Despite this showing above, the Examiner indicates that the “unexpected result that was tested with two specific species (i.e., decanoyl or ethylhexanoyl) can not be used to represent the sub-genus of the claimed invention.” Accordingly, to demonstrate the unexpected advantages flowing from the full range of claimed sub-genus, Applicants **submit herewith a Declaration** under 37 C.F.R. §1.132, which is summarized below for the Examiner’s convenience.

In section (A) of paragraph 5 of the Declaration under 37 C.F.R. §1.132, Applicants have shown the correlation between a length of the acyl chain of the acylamino acid dibutylamide and gel forming ability. In this experiment, the gel forming ability of several acylamino acid dibutylamides, each having an acyl chain with a different number of carbon atoms, was tested using isopropyl myristate (IPM), trioctanoic acid glyceride (TOG), liquid paraffin, and a mixed oil containing Cyclometicon and octyldodecanol (SH-OD). The results of this experiment reveal that the acyl group having 8 to 10 carbon atoms provided superior gel forming ability to an acyl group having 6 carbon atoms or less (almost no gel forming ability) and the acyl group having 12 carbon atoms or more (low gel forming ability). Further, when the experiment was performed in a silicone oil (such as exemplified by SH-OD containing "Cyclometicon"), which is frequently used in the field of cosmetics, the acyl group having 8 to 10 carbon atoms provided particularly excellent results as compared to acyl groups having 6 carbon atoms or less and acyl groups having 12 carbon atoms or more (see paragraph 5, part (A) of the Declaration under 37 C.F.R. §1.132).

From the foregoing results it is apparent that an acyl group having 8 to 10 carbon atoms specifically possesses higher gel forming ability than a higher lipophilic acyl group with longer acyl chain or than a shorter acyl group. As the Declarant states, these results are quite surprising, because it would have been generally believed by one of ordinary skill in the art that a more lipophilic gelling agent would possess a higher gel forming ability (see paragraph 5, part (A) of the Declaration under 37 C.F.R. §1.132). It is also quite surprising that the acyl groups having 6 carbon atoms or less give only poor results. Further, EH, which has a branched acyl chain and exists as a mixture of two diastereomers, gave a superior result to a gelling agent having a straight acyl chain (see paragraph 5, part (A) of the Declaration under 37 C.F.R. §1.132). This result is also very surprising because one of ordinary skill in the art would have

believed that EH as a mixture of two diastereomer would only result in poor gel forming ability due to the mixture of two different compounds (see paragraph 5, part (A) of the Declaration under 37 C.F.R. §1.132).

It is again noted that Hofrichter et al (U.S. Patent No. 5,591,424) specifically discloses that "Particularly preferred are n-acyl glutamic acid amides and n-acyl glutamic acid esters corresponding to the following formula:



wherein R<sub>1</sub> is an alkyl, aryl, arylalkyl radical (branched, linear or cyclic), having from about 1 to about 26 carbon atoms; preferably, from about 6 to about 22 carbon atoms, more preferably, from about 12 to about 18 carbon atoms." Accordingly, the inventors of Hofrichter et al clearly consider that R<sub>1</sub> groups having 12 to 18 carbon atoms are preferred. Accordingly, in view of the disclosure of Hofrichter et al, one of ordinary skill in the art would not have been motivated to select an acyl group having 8 to 10 carbon atoms to obtain a gelling agent of the present invention having excellent gel forming ability.

Further, in part (B) of the Declaration under 37 C.F.R. §1.132, Applicants discuss the synergistic effect of EH and N-Lauroyl-L-glutamic acid dibutylamide (GP-1) in gel forming ability as well as in transparency, which is demonstrated in Examples 7 to 10 of the present specification. It is generally expected that a contamination of an exogenous substance in a gel would result in extensive break of gel network and significant reduction of gel forming ability of a gelling agent. This phenomenon is observed in a mixed system containing EH and GP-1;

however, as shown by the results shown in the figure, the mixture of a ratio around 2/2 (ratios from 3/1 to 1/3) gave practically sufficient gel forming ability (sufficient gel strength), and moreover, the appearance of the gelled oil formed by using the mixture in the above ratio was semitransparent or transparent (see paragraph 5, part (B) of the Declaration under 37 C.F.R. §1.132). This result was very surprising because an ordinary mixed gelling agent generally fails to give a semitransparent or transparent gel due to weakened gel strength (see paragraph 5, part (B) of the Declaration under 37 C.F.R. §1.132). Such a result is not expected based on the disclosure of Hofrichter et al.

In view of the foregoing, Applicants submit that the present invention is not obvious in view of Hofrichter et al. Accordingly, Applicants request acknowledgement that this ground of rejection has been withdrawn.

With respect to the non-elected claims, Applicants note that these claims depend directly from the elected compound claims. As such, the elected compounds are required elements of the non-elected claims. Therefore, if the compound claims are found allowable, these compounds would necessarily impart novelty upon the non-elected claims and they too should be found allowable.

Application Serial No. 10/073,226

Response to Office Action of March 10, 2004 and the Advisory Action dated August 16, 2004

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,  
MAIER & NEUSTADT, P.C.



Masayasu Mori  
Registration No. 47,301

Vincent K. Shier, Ph.D.  
Registration No. 50,552

Customer Number

**22850**

Tel: (703) 413-3000  
Fax: (703) 413-2220  
(OSMMN 08/03)  
NFO:VKS